1: J Virol 1994 Oct;68(10):6347-62 Related Articles, Links

Improved cell survival by the reduction of immediate-early gene expression in replication-defective mutants of herpes simplex virus type 1 but not by mutation of the virion host shutoff function.

Johnson PA, Wang MJ, Friedmann T.

Department of Pediatrics, University of California, San Diego, La Jolla 92093-0634.

Derivatives of herpes simplex virus type 1 (HSV-1) have elicited considerable interest as gene transfer vectors because of their ability to infect a wide range of cell types efficiently, including fully differentiated neurons. However, it has been found that infection of many types of cell with vectors derived from replication-defective mutants of HSV-1 is associated with cytopathic effects (CPE). We have previously shown that viral gene expression played an important role in the induction of CPE caused by an HSV-1 mutant deleted for the essential immediate-early gene 3 (IE 3) (P.A. Johnson, A. Miyanohara, F. Levine, T. Cahill, and T. Friedmann, J. Virol. 66:2952-2965, 1992). We have investigated which viral genes might be responsible for CPE by comparing the ability of each of the individual genes expressed by an IE 3 deletion mutant during a nonproductive infection to inhibit biochemical transformation after cotransfection of BHK or CV-1 cells with a selectable marker gene. Transfection of IE genes 1,2, and 4 individually all caused a marked inhibition of colony formation, while transfection of IE 5 and the large subunit of ribonucleotide reductase had little effect. These results suggested that it would be necessary to mutate or reduce the expression of nearly all HSV-1 IE genes to reduce virus-induced CPE. Therefore, we have used VP16 mutants, which are unable to transinduce IE gene expression (C. I. Ace, T. A. McKee, J. M. Ryan, J. M. Cameron, and C. M. Preston, J. Virol. 63:2260-2269, 1989), to derive two replication-defective strains: 14H delta 3, which is deleted for both copies of IE 3, and in 1850 delta 42, which has a deletion in the essential early gene UL42. The IE 3-VP16 double mutant, 14H delta 3, is significantly less toxic than a single IE 3 deletion mutant over a range of multiplicities of infection, as measured in a cell-killing assay, and has an enhanced ability to persist in infected cells in a biologically retrievable form. In contrast, the UL42-VP16 double mutant, in 1850 delta 42, showed reduced toxicity only at low multiplicities of infection. To test the role of the virion host shutoff function as an additional candidate to influence virus-induced CPE, we have introduced a large insertion mutation into the virion host shutoff gene of an IE 3 deletion mutant and the double mutant 14H delta 3.(ABSTRACT TRUNCATED AT 400 WORDS)

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L2: Entry 6 of 6 File: DWPI Jul 3, 2001

DERWENT-ACC-NO: 2001-408653
DERWENT-WEEK: 200164

TITLE: Use of replication incompetent herpes virus having mutation that prevents 2 immediate early genes expression, and heterologous gene linked to promoter active during herpes virus latency, to treat Parkinson's disease

INVENTOR: COFFIN, R S

PRIORITY-DATA: 1999GB-0030418 (December 22, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 200120175 A	July 3, 2001		000	C12N015/86
WO 200146449 A1	June 28, 2001	E	042	C12N015/86

INT-CL (IPC): A61 K 48/00; A61 P 25/00; A61 P 25/16; A61 P 25/28; C12 N 15/86; G01 N 33/50

ABSTRACTED-PUB-NO: WO 200146449A
BASIC-ABSTRACT:

NOVELTY - Use of replication incompetent herpes virus (I) having mutation that prevents/reduces 2 immediate early genes expression, and heterologous gene linked to promoter active during herpes virus latency, for:

(a) preparing medicament to treat/prevent CNS disorder (CD);

(b) determining effect of gene on phenotype associated with CD or on CNS cell that is relevant to CD; and

(c) treating/preventing CD in a subject.

DETAILED DESCRIPTION - Use of replication incompetent herpes virus (I) comprising mutation which prevents or reduces expression of two immediate early genes, and heterologous gene operably linked to promoter active during herpes virus latency for:

(a) manufacturing medicament for treating or preventing central nervous system (CNS) disorder;

(b) determining whether a gene has effect on phenotype associated with CNS disorder or on cell of CNS which is relevant to the disorder;

(c) treating or preventing a subject from CNS disorder.

Determining (M1) whether a gene has an effect on a phenotype associated with CD or on a cell of CNS which is relevant to a CD, involves inoculating into a cell of the CNS with (I) and monitoring a phenotype of the disorder or an effect of expression of the gene on the cell to determine whether the gene has an effect on the cell or the phenotype. Treating a subject suffering from CD or of preventing a CD in a subject who

is at risk of developing a disorder involves administering (I).

An INDEPENDENT CLAIM is also included for an agent for treating or preventing a CD comprising (I).

ACTIVITY - Nootropic; neuroprotective; antiparkinsonian; cerebroprotective.

No supporting data is given.

MECHANISM OF ACTION - Gene therapy.

USE - Preparing medicament to treat/prevent CD such as Alzheimer's disease, Parkinson's disease, stroke, Tay-Sachs disease, determining effect of gene on phenotype associated with CD or on CNS cell that is relevant to CD, treating/preventing CD in a subject. (M1) is useful for screening genes implicated in CD, to identify a target for gene therapy or for small molecule modulators (claimed). The viruses are useful for treating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, stroke, Tay-Sachs disease. The viruses are thus used to deliver therapeutic genes to treat central nervous system. Administration of the herpes virus vector to a subject suffering from disorder of CNS typically alleviates the symptoms of the disorder and/or prevents the progression of the disorder. Replication incompetent virus strain 1764/27-/4-/pR191lacZ was a virus with the in1814 mutation in the gene encoding VMW65 and with the genes encoding ICP34.5 and open reading frame (ORF) P completely deleted. The term 27- refers to the deletion of nucleotides 113273-116869, which contain the genes UL54, 55 and 56. UL54 was the gene encoding the essential immediate early (IE) gene ICP27 and UL55 and 56 were both non-essential genes. Hence, 1764/27-/4- virus was deleted for ICP34.5, ICP27 and ICP4 with an inactivating mutation in vmw65 as for virus strain 1764/27-/4-/PR20.5 (Thomas et al., 1999). This virus also contains a cytomegalovirus (CMV) promoter (from pcDNA3)/lacZ(pCHI10)/PolyA cassette inserted into both copies of the LAT region between the BstXI sites at nts 120,219 and 120,413. Before insertion of the CMV/lacZ cassette in 1764/27-/4-/pR19lacZ, the lacZ/green fluorescent protein (GFP) insertion into ICP4 in 1764/27-/4-/pR20.5 was removed by recombination with empty ICP4 flanking regions and selection of virus plaques which did not express lacZ or GFP giving virus strain 1764/27-/4-w. Virus strain 17+/pR19lacZ contains an identical insertion into the latency associated transcripts (LAT) region as in virus strain 1764/27-/4-/pR19lacZ, was disabled only by the deletion of ICP27. Virus strain 1764/27-/4-/CMVlacZ/US5 contains a CMV/lacZ/polyA insertion into the unique SacI site in the non-essential US5 gene of 1764/27-/4-/w. Virus stains 1764/27- and 1764/27-/4- were also deleted for the endogenous LAT P2 regions in order to prevent the recombinational instability. Injections into the rat striatum, spinal cord or superior colliculus were carried out with the 1764/27-/4-/pR19lacZ. 5 mu l of virus strain 1764/27-/4-/pRI9lacZ at a titer of 1/ asterisk 108 plaque forming units (pfu)/ml was inoculated into the striatum of 20-220 g female Lewis rats and brains removed and sectioned. Brain sections showed high efficiency gene delivery in the striatum at 3 days post-inoculation with large numbers of X-gal staining cells also evident at 1 week and 1 month after inoculation. Significant X-gal staining was observed in the substantia nigra. Therefore, using both a replication incompetent virus backbone in which IE gene expression had been minimized and a promoter active during virus latency, gene delivery was observed at both the inoculated site within the brain, in this case the striatum, and also at connected sites such as in this case the substantia nigra. In order to test the ability of 1764 27-4- viruses to deliver exogenous genes to cultured neurons, primary cultures of dorsal root ganglion ((DRG) neurons were infected at an multiplicity of infection (MOI) of 10 with 1764/27-/4-/pR20.5. Neurons infected with the 1764/27-/4- virus expressed abundant levels of GFP, in both neuronal cell bodies and processes demonstrating efficient gene delivery.

ADVANTAGE - (I) gives highly efficient gene delivery to multiple regions within the brain following vector inoculation to only a single brain region which results from highly efficient retrograde transport of the vectors to cell bodies at the connected sites. (I) also is incapable of replicating in any cell unless at least one gene which has been rendered non functional in the virus is also expressed in the cell, e.g., the virus is replication incompetent other than in the cells in which virus stocks are prepared. Adult Lewis rats were stereotaxically injected with 2.5 multiply 105 pfu of

1764/27-/4-/pR19lacZ at the C6 level of the spinal cord or into the superior colliculus and thalamus. Three weeks after injection, the animals were perfusion fixed and relevant areas of the nervous system were sectioned and stained for lacZ expression. The virus gave high level gene expression at the site of injection and was also efficiently transported from the site of injection to the cell bodies at connected sites where gene expression occurred. This was clearly demonstrated by the transport of the disabled virus from the striatum to the substantia nigra, from the superior colliculus via the optic nerve to the retinal ganglion cells, and from the C6 level of the spinal cord to dorsal root ganglions (DRGs), the brain stem and areas of the hind and midbrain.

ABSTRACTED-PUB-NO: WO 200146449A
EQUIVALENT-ABSTRACTS:

CHOSEN-DRAWING: Dwg.0/0

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IFIUDB
 NEWS  6  Apr 22   Records from IP.com available in CAPLUS, HCAPLUS, and
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 NEWS  8  Apr 22   Federal Research in Progress (FEDRIP) now available
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 NEWS EXPRESS  October 14 CURRENT WINDOWS VERSION IS V6.01,
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               AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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=> "HSV mutant"
          9071 "HSV"
            32 "HSVS"
          9073 "HSV"
                 ("HSV" OR "HSVS")
        156056 "MUTANT"
        100979 "MUTANTS"
        206845 "MUTANT"
                 ("MUTANT" OR "MUTANTS")
L1          79 "HSV MUTANT"
                 ("HSV"(W)"MUTANT")

=> vmw65 or VP16 or TIF
           347 VMW65
          1573 VP16
           678 TIF
            29 TIFS
           698 TIF
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(TIF OR TIFS)
L2 2355 VMW65 OR VP16 OR TIF

=> L2 and L1
L3 3 L2 AND L1

=> ICP4 and L1
499 ICP4
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L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:239298 CAPLUS
DOCUMENT NUMBER: 128:279564
TITLE: Herpes simplex virus attenuated strains with modified immediate early genes
INVENTOR(S): DeLuca, Neal A.
PATENT ASSIGNEE(S): University of Pittsburgh of the Commonwealth System of Higher Education, USA; DeLuca, Neal A.
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9815637	A1	19980416	WO 1997-US8681	19970522
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5804413	A	19980908	US 1996-651419	19960522
AU 9731379	A1	19980505	AU 1997-31379	19970522
EP 904395	A1	19990331	EP 1997-926668	19970522
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, IE, FI				
JP 2001503611	T2	20010321	JP 1998-512036	19970522
US 6261552	B1	20010717	US 1998-194274	19981120
US 2001026799	A1	20011004	US 2001-829839	20010410

PRIORITY APPLN. INFO.:
US 1996-651419 A2 19960522
US 1992-922839 B1 19920731
US 1994-342795 A2 19941121
US 1995-479024 A2 19950607
WO 1997-US8681 W 19970522
US 1998-194274 A1 19981120

AB The present invention provides an HSV having a genome from which, in the presence of the **ICP4** gene product, a native immediate early gene is expressed with delayed kinetics, and an HSV having a genome with a

mutation in each of the genes encoding **ICP4**, ICP27, and another HSV gene. Preferably, such HSV will also encode one or more exogenous genes. The present invention further provides a method of expressing a polynucleotide within a cell comprising infecting the cell with such an HSV. Furthermore, the present invention provides a cell line having DNA encoding the HSV proteins **ICP4**, ICP27, and ICP0, and a method of producing an HSV vector by employing such a cell line. The expression kinetics of any or all of the immediate early gene products can be delayed, such that the vector avoids the .apprx.5-10-fold decrease in viral titer assocd. with their expression in packaging cell lines. Attenuated immediate early gene expression can be achieved by mutation of viral sequences comprising the **VP16**-Oct1 consensus TAATGARAT sequence present within the inverted repeat regions of the HSV genome. These **HSV mutant** strains have characteristics amenable to use as gene transfer vehicles, including (1) the ability to obtain large quantities of recombinant virus, (2) a significant redn. in wild-type reversion, (3) an ability to accept larger foreign DNA fragments for gene transfer applications, (4) minimized interference with host cell protein synthesis, and (5) reduced or even minimal host cell cytotoxicity.

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L4 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:217573 CAPLUS
DOCUMENT NUMBER: 131:72363
TITLE: Immunogenicity of Herpes Simplex Virus Type 1 Mutants Containing Deletions in One or More .alpha.-Genes: **ICP4**, ICP27, ICP22, and ICP0
AUTHOR(S): Brehm, Michael; Samaniego, Lorna A.; Bonneau, Robert H.; DeLuca, Neal A.; Tevethia, Satvir S.
CORPORATE SOURCE: Department of Microbiology and Immunology, The Pennsylvania State University College of Medicine, Hershey, PA, 17033, USA
SOURCE: Virology (1999), 256(2), 258-269
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Replication defective mutants of HSV have been proposed both as vaccine candidates and as vehicles for gene therapy because of their inability to produce infectious progeny. The immunogenicity of these HSV replication mutants, at both qual. and quant. levels, will directly det. their effectiveness for either of these applications. We have previously reported (Brehm et al., J. Virol., 71, 3534, 1997) that a replication defective mutant of HSV-1, which expresses a substantial level of viral genes without producing virus particles, is as efficient as wild-type HSV-1 in eliciting an HSV-specific cytotoxic T-lymphocyte (CTL) response. In this report, we have further evaluated the immunogenic potential of HSV-1-derived replication defective mutants by examg. the generation of HSV-specific CTL following immunization with viruses that are severely restricted in viral gene expression due to mutations in one or more HSV .alpha. genes (**ICP4**, ICP27, ICP22, and ICP0). To measure the CTL responses induced by the HSV .alpha.-mutants, we have targeted two H-2Kb-restricted CTL epitopes: an epitope in a virion protein, gB

(498-505), and an epitope in a nonvirion protein, ribonucleotide reductase
(RR1 822-829). The **HSV mutants** used in this study are impaired in their ability to express gB while a majority of them still express RR1. Our findings demonstrate that a single immunization with these mutants is able to generate a strong CTL response not only to RR1 822-829, but also to gB498-505 despite their inability to express wild-type levels of gB. Furthermore, a single immunization with any individual mutant can also provide immune protection against HSV challenge. These results suggest that mutants which are restricted in gene expression may be used as effective immunogens in vivo. (c) 1999 Academic Press.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:181441 CAPLUS
DOCUMENT NUMBER: 130:320417
TITLE: Transcription of herpes simplex virus immediate-early and early genes is inhibited by Roscovitine, an inhibitor specific for cellular cyclin-dependent kinases
AUTHOR(S): Schang, Luis M.; Rosenberg, Amy; Schaffer, Priscilla A.
CORPORATE SOURCE: Department of Microbiology, University of Pennsylvania
School of Medicine, Philadelphia, PA, 19104-6076, USA
SOURCE: Journal of Virology (1999), 73(3), 2161-2172
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although herpes simplex virus (HSV) replicates in noncycling as well as cycling cells, including terminally differentiated neurons, it has recently been shown that viral replication requires the activities of cellular cyclin-dependent kinases (cdks) (L. M. Schang, J. Phillips, and P. A. Schaffer, J. Virol. 72:5626-5637, 1998). Since the authors were unable to isolate **HSV mutants** resistant to two cdk inhibitors, Olomoucine and Roscovitine (Rosco), the authors hypothesized that cdks may be required for more than one viral function during HSV replication. In the expts. presented here, the authors tested this hypothesis by measuring the efficiency of (i) viral replication; (ii) expression of selected immediate-early (IE) (ICP0 and **ICP4**), early (E) (ICP8 and TK), and late (L) (gC) genes; and (iii) viral DNA synthesis in infected cultures to which Rosco was added after IE or IE and
E proteins had already been synthesized. Rosco inhibited HSV replication,
transcription of IE and E genes, and viral DNA synthesis when added at 1, 2, or 6 h postinfection or after release from a 6-h cycloheximide block. Transcription of a representative L gene, gC, was also inhibited by Rosco under all conditions examd. The authors conclude from these studies that cellular cdks are required for transcription of E as well as IE genes. In
contrast, steady-state levels of at least one cellular housekeeping gene were not affected by Rosco. The requirement of viral IE and E transcription for cellular cdks may reflect either a requirement for specific cdk-activated cellular and/or viral transcription factors or a

more global requirement for cdks in the transcriptional activation of the viral genome.

REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:395616 CAPLUS
DOCUMENT NUMBER: 129:120934
TITLE: Requirement for cellular cyclin-dependent kinases in herpes simplex virus replication and transcription
AUTHOR(S): Schang, Luis M.; Phillips, Joanna; Schaffer, Priscilla A.
CORPORATE SOURCE: Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104-6076, USA
SOURCE: Journal of Virology (1998), 72(7), 5626-5637
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several observations indicate that late-G1/S-phase-specific cellular functions may be required for herpes simplex virus (HSV) replication: (i) certain mutant HSV strains are replication impaired during infection of cells in the G0/G1 but not in the G1/S phase of the cell cycle, (ii) several late-G1/S-phase-specific cellular proteins and functions are induced during infection, and (iii) the activity of a cellular protein essential for expression of viral immediate-early (IE) genes, HCF, is normally required during the late G1/S phase of the cell cycle. To test the hypothesis that late-G1/S-phase-specific cellular functions are necessary for HSV replication, HEL or Vero cells were infected in the presence of the cell cycle inhibitors roscovitine (Rosco) and olomoucine (Olo). Both drugs inhibit cyclin-dependent kinase 1 (cdk-1) and cdk-2 (required for cell cycle progression into the late G1/S phase) and cdk-5 (inactive in cycling cells) but not cdk-4 or cdk-6 (active at early G1). The authors found that HSV replication was inhibited by Rosco and Olo but not by lovastatin (a cell cycle inhibitor that does not inhibit cdk activity), staurosporine (a broad-spectrum protein serine-threonine kinase inhibitor), PD98059 (an inhibitor specific for erk-1 and -2) or iso-Olo (a structural isomer of Olo that does not inhibit cdk activity). The concns. of Rosco and Olo required to inhibit cell cycle progression and viral replication in both HEL and Vero cells were similar. Inhibition of viral replication was found not to be mediated by drug-induced cytotoxicity. Efforts to isolate Rosco- or Olo-resistant **HSV mutants** were unsuccessful, indicating that these drugs do not act by inhibiting a single viral target. Viral DNA replication and accumulation of IE and early viral RNAs were inhibited in the presence of cell cycle-inhibitory concns. of Rosco or Olo. The authors therefore conclude that one or more cdks active from late G1 onward or inactive in nonneuronal cells are required for accumulation of HSV transcripts, viral DNA replication, and prodn. of infectious virus.

L4 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:239298 CAPLUS
DOCUMENT NUMBER: 128:279564

TITLE: Herpes simplex virus attenuated strains with modified immediate early genes

INVENTOR(S): DeLuca, Neal A.

PATENT ASSIGNEE(S): University of Pittsburgh of the Commonwealth System of Higher Education, USA; DeLuca, Neal A.

SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9815637	A1	19980416	WO 1997-US8681	19970522
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5804413	A	19980908	US 1996-651419	19960522
AU 9731379	A1	19980505	AU 1997-31379	19970522
EP 904395	A1	19990331	EP 1997-926668	19970522
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, IE, FI				
JP 2001503611	T2	20010321	JP 1998-512036	19970522
US 6261552	B1	20010717	US 1998-194274	19981120
US 2001026799	A1	20011004	US 2001-829839	20010410

PRIORITY APPLN. INFO.:

US 1996-651419	A2	19960522
US 1992-922839	B1	19920731
US 1994-342795	A2	19941121
US 1995-479024	A2	19950607
WO 1997-US8681	W	19970522
US 1998-194274	A1	19981120

AB The present invention provides an HSV having a genome from which, in the presence of the **ICP4** gene product, a native immediate early gene is expressed with delayed kinetics, and an HSV having a genome with a mutation in each of the genes encoding **ICP4**, ICP27, and another HSV gene. Preferably, such HSV will also encode one or more exogenous genes. The present invention further provides a method of expressing a polynucleotide within a cell comprising infecting the cell with such an HSV. Furthermore, the present invention provides a cell line having DNA encoding the HSV proteins **ICP4**, ICP27, and ICP0, and a method of producing an HSV vector by employing such a cell line. The expression kinetics of any or all of the immediate early gene products can be delayed, such that the vector avoids the .apprx.5-10-fold decrease in viral titer assocd. with their expression in packaging cell lines. Attenuated immediate early gene expression can be achieved by mutation of viral sequences comprising the VP16-Oct1 consensus TAATGARAT sequence present within the inverted repeat regions of the HSV genome. These **HSV mutant** strains have characteristics amenable to use as gene transfer vehicles, including (1) the ability to obtain large quantities of recombinant virus, (2) a significant redn. in wild-type reversion, (3) an ability to accept larger foreign DNA fragments for gene transfer applications, (4) minimized interference with host cell protein synthesis, and (5) reduced or even minimal host cell cytotoxicity.

LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 5804413	A	19980908	US 1996-651419	19960522	
AU 9731379	A1	19980505	AU 1997-31379	19970522	
EP 904395	A1	19990331	EP 1997-926668	19970522	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, IE, FI					
JP 2001503611	T2	20010321	JP 1998-512036	19970522	
US 6261552	B1	20010717	US 1998-194274	19981120	
US 2001026799	A1	20011004	US 2001-829839	20010410	

PRIORITY APPLN. INFO.:	US 1996-651419	A2 19960522
	US 1992-922839	B1 19920731
	US 1994-342795	A2 19941121
	US 1995-479024	A2 19950607
	WO 1997-US8681	W 19970522
	US 1998-194274	A1 19981120

AB The present invention provides an HSV having a genome from which, in the presence of the ICP4 gene product, a native immediate early gene is expressed with delayed kinetics, and an HSV having a genome with a mutation in each of the genes encoding ICP4, ICP27, and another HSV gene. Preferably, such HSV will also encode one or more exogenous genes. The present invention further provides a method of expressing a polynucleotide within a cell comprising infecting the cell with such an HSV. Furthermore, the present invention provides a cell line having DNA encoding the HSV proteins ICP4, ICP27, and ICP0, and a method of producing an HSV vector by employing such a cell line. The expression kinetics of any or all of the immediate early gene products can be delayed, such that the vector avoids the .apprx.5-10-fold decrease in viral titer assocd. with their expression in packaging cell lines. Attenuated immediate early gene expression can be achieved by mutation of viral sequences comprising the **VP16**-Oct1 consensus TAATGARAT sequence present within the inverted repeat regions of the HSV genome. These **HSV mutant** strains have characteristics amenable to use as gene transfer vehicles, including (1) the ability to obtain large quantities of recombinant virus, (2) a significant redn. in wild-type reversion, (3) an ability to accept larger foreign DNA fragments for gene transfer applications, (4) minimized interference with host cell protein synthesis, and (5) reduced or even minimal host cell cytotoxicity.

L3 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:	1996:437420 CAPLUS
DOCUMENT NUMBER:	125:106982
TITLE:	Gene delivery to the heart in vivo and to cardiac myocytes and vascular smooth muscle cells in vitro using herpes virus vectors
AUTHOR(S):	Coffin, R. S.; Howard, M. K.; Cumming, D. V. E.; Dollery, C. M.; McEwan, J.; Yellon, D. M.; Marber, M. S.; MacLean, A. R.; Brown, S. M.; Latchman, D. S.
CORPORATE SOURCE:	Dep. Molecular Pathology, Univ. Coll. London Med. Sch., London, W1A 6DB, UK
SOURCE:	Gene Therapy (1996), 3(7), 560-566 CODEN: GETHEC; ISSN: 0969-7128

PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Herpes simplex virus 1 (HSV1), while usually thought of as neurotrophic, can also efficiently infect a wide variety of non-neuronal cell types and so might be developed as a vector for gene delivery to non-neuronal as well as neuronal cells. Here we have tested three different disabled HSV vectors for their ability to deliver a lacZ gene to primary cardiac myocytes and vascular smooth muscle cells in vitro, and used the most efficient virus to transect the rat heart in vivo. We also assessed the degree of cytopathic effect of the various viruses on the cardiac myocytes in vitro by testing the effects on the frequency of beating in synchronously beating myocyte cultures. While an **HSV mutant** in which the essential immediate-early gene IE2 had been deleted gave high efficiency gene transfer to the cardiac myocytes in vitro and the rat heart in vivo, viruses in which ICP34.5 or ICP34.5 and **VMW65** were inactive (and which were also unable to replicate in these cells) gave a much lower efficiency of gene transfer mirroring the degree of cytopathic effect obsd. in the beating myocyte cultures. Gene transfer to the vascular smooth muscle cells was considerably less efficient than to the myocytes in all cases. These results indicate that while HSV may be inappropriate for highly efficient gene transfer to the arterial wall, efficient gene transfer can be achieved in the myocardium, and thus that HSV vectors may be suitable for the alteration of cardiac cells physiol. in vivo.

=> in1814 and ICP4
22 IN1814
499 ICP4
L6 5 IN1814 AND ICP4

=> L1 and L6
L7 0 L1 AND L6

=> DIS L6 1- IBIB ABS
YOU HAVE REQUESTED DATA FROM 5 ANSWERS - CONTINUE? Y/(N):Y
THE ESTIMATED COST FOR THIS REQUEST IS 11.45 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L6 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:465467 CAPLUS
DOCUMENT NUMBER: 127:172797
TITLE: Truncation of the C-terminal acidic transcriptional activation domain of herpes simplex virus VP16 produces a phenotype similar to that of the **in1814** linker insertion mutation
AUTHOR(S): Smiley, James R.; Duncan, Joanne
CORPORATE SOURCE: Cancer Research Group, Institute for Molecular Biology and Biotechnology, Pathology Dep., McMaster University, Hamilton, ON, L8N 3Z5, Can.
SOURCE: Journal of Virology (1997), 71(8), 6191-6193
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We examd. the phenotype of a herpes simplex virus (HSV) type 1 mutant (V422) in which the C-terminal acidic activation domain of the virion

transactivator VP16 is truncated at residue 422. The efficacy of plaque formation by V422 on Vero cells was boosted by approx. 100-fold by including hexamethylene bisacetamide (HMBA) in the growth medium, as previously obsd. with the **in1814** VP16 linker insertion mutant isolated by Preston and colleagues. V422 displayed severely reduced levels of the immediate-early transcripts encoding ICP0 and **ICP4** during infection in the presence of cycloheximide, and this defect was partially overcome by the addn. of HMBA. The defect in plaque formation exhibited by V422 and **in1814** was efficiently complemented in U2OS osteosarcoma cells, which had previously been shown to complement ICP0 null mutations. Taken in combination, these data confirm the key role of VP16 in triggering the onset of the HSV lytic cycle.

L6 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:166697 CAPLUS
DOCUMENT NUMBER: 126:248709
TITLE: Construction and characterization of herpes simplex virus type 1 mutants with conditional defects in immediate early gene expression
AUTHOR(S): Preston, Chris M.; Mabbs, Russell; Nicholl, Mary Jane
CORPORATE SOURCE: MRC Virology Unit, Inst. Virology, Glasgow, G11 5JR, UK
SOURCE: Virology (1997), 229(1), 228-239
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The herpes simplex virus type 1 (HSV-1) mutant **in1814** contains an insertion mutation in the coding sequence for the virion transactivator protein VP16 and is thus impaired for the activation of immediate early (IE) gene expression. This virus was modified further by introducing the Moloney murine leukemia virus LTR promoter in place of the upstream sequences controlling expression of the IE regulatory protein ICP0, to yield mutant in1820. In almost all cell types tested, in1820 initiated infection less efficiently than **in1814**, behaving as if lacking both VP16 and ICP0 functions, but in BHK cells in1820 was less impaired than **in1814**. A rescuant of in1820 at the VP16 locus, in1825, also exhibited a host range phenotype, initiating replication as efficiently as wild-type HSV-1 in BHK cells but inefficiently in other cell types. In1825 was unable to complement an ICP0 null mutant in restricted cells, demonstrating that the promoter exchange prevented the expression of ICP0 protein in functionally significant amts. The novel host range properties of in1820 provided a basis for the construction of addnl. viruses conditionally impaired for IE gene expression and assessment of their value as prototype vectors. Prodn. of an HSV-1 mutant multiply defective in the expression of IE gene products was achieved by introduction of the temp.-sensitive mutation of HSV-1 tsK, which inactivates the IE transcription activator **ICP4** at nonpermissive temps., into in1820 to produce in1820K. This mutant could be propagated effectively in BHK cells at 31.degree. but was effectively devoid of the major regulators ICP0, **ICP4**, and VP16 in other cells types at 38.5.degree.. Cultures could withstand infection with 5 PFU of in1820K per cell without detectable cytopathol. and could be reseeded to form colonies at approx. 90% efficiency. A deriv. of in1820K contg. the Escherichia coli lacZ gene controlled by the human cytomegalovirus (HCMV) major IE promoter expressed low but detectable levels of .beta.-galactosidase in almost all cells after infection of cultures at 5 PFU per cell and incubation at 38.5.degree.. Cultures infected with 5 PFU

per cell of an in1820K deriv. expressing neomycin phosphotransferase (npt) controlled by the HCMV IE promoter were resistant to killing by the antibiotic G418 for up to 3 days, and cell survival correlated with the retention of functional levels of npt. Mutants based on in1820K can thus express foreign gene products in virtually all cells in a culture under conditions in which cytotoxicity is eliminated, demonstrating that progressive redn. of IE gene expression is an important step in the design of HSV-1-derived vectors.

L6 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:597121 CAPLUS
DOCUMENT NUMBER: 119:197121
TITLE: Varicella-zoster virus (VZV) open reading frame 61 protein transactivates VZV gene promoters and enhances the infectivity of VZV DNA
AUTHOR(S): Moriuchi, Hiroyuki; Moriuchi, Masako; Straus, Stephen E.; Cohen, Jeffrey I.
CORPORATE SOURCE: Lab. Clin. Invest., Natl. Inst. Allergy Infect. Dis., Bethesda, MD, 20892, USA
SOURCE: Journal of Virology (1993), 67(7), 4290-5
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The varicella-zoster virus (VZV) open reading frame 61 (ORF61) protein is the homolog of herpes simplex virus type (HSV-1) IC90. Both genes are located in similar parts of the genome, their predicted products share a cysteine-rich motif, and cell lines expressing VZV ORF61 are able to complement an HSV-1 ICP0 deletion mutant (Moriuchi, H., et al., 1992). In transient expression assays, HSV-1 ICP0 is a transactivator alone and transactivates in synergy with another viral transactivator, **ICP4**. However, VZV ORF61 represses the activation by VZV-encoded proteins ORF62 (the homolog of **ICP4**) and ORF4. To further characterize the function of VZV ORF61 and its role(s) in regulation of viral gene expression, the authors performed transient expression assays using target promoters from VZV, HSV-1, and unrelated viruses. In the absence of other viral activators, VZV ORF61 transactivated most promoters tested. In addn., a cell line stably expressing VZV ORF61 complemented the HSV-1 mutant **in1814**, which lacks the transactivating function of VP16. The cell line expressing VZV ORF61 enhanced the infectivity of HSV-1 virion DNA. Moreover, transient expression of VZV ORF61 also enhanced the infectivity of HSV-1 virion DNA. These results indicate that VZV ORF61 can stimulate expression of HSV-1 and VZV genes at an early stage in the viral replicative cycle and that ORF61 has an important role in VZV gene regulation.

L6 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:249229 CAPLUS
DOCUMENT NUMBER: 118:249229
TITLE: Varicella-zoster virus open reading frame 10 protein, the herpes simplex virus VP16 homolog, transactivates herpesvirus immediate-early gene promoters
AUTHOR(S): Moriuchi, Hiroyuki; Moriuchi, Masako; Straus, Stephen E.; Cohen, Jeffrey I.

CORPORATE SOURCE: Lab. Clin. Invest., Natl. Inst. of Allergy and Infect.
Dis., Bethesda, MD, 20892, USA
SOURCE: Journal of Virology (1993), 67(5), 2739-46
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The varicella-zoster virus (VZV) open reading frame 10 (ORF10) protein is the homolog of the herpes simplex virus type 1 (HSV-1) protein VP16. These are two virion tegument proteins that have extensive amino acid sequence identity in their amino-terminal and middle domains. ORF10, however, lacks the acidic carboxy terminus which is crit. for transactivation by VP16. Earlier studies showed that VZV ORF10 does not form a tertiary complex with the TAATGARAT regulatory element (where R is a purine) with which HSV-1 VP16 interacts, suggesting that ORF10 may not have transactivating ability. Using transient-expression assays, it is shown that VZV ORF10 is able to transactivate VZV immediate-early (IE) gene (ORF62) and HSV-1 IE gene (**ICP4** and ICP10) promoters. Furthermore, cell lines stably expressing ORF10 complement the HSV-1 mutant **in1814**, which lacks the transactivating function of VP16, and enhance the de novo synthesis of infectious virus following transfection of HSV-1 virion DNA. These results indicate that ORF10, like its HSV-1 homolog VP16, is a transactivating protein despite the absence of sequences similar to the VP16 carboxy-terminal domain. The transactivating function of the VZV ORF10 tegument protein may be crit. for efficient initiation of viral infection.

L6 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:200602 CAPLUS
DOCUMENT NUMBER: 114:200602
TITLE: Investigation of herpes simplex virus type 1 (HSV-1) gene expression and DNA synthesis during the establishment of latent infection by an HSV-1 mutant, **in1814**, that does not replicate in mouse trigeminal ganglia
AUTHOR(S): Valyi-Nagy, Tibor; Deshmane, Satish L.; Spivack, Jordan G.; Steiner, Israel; Ace, Chris I.; Preston, Chris M.; Fraser, Nigel W.
CORPORATE SOURCE: Wistar Inst., Philadelphia, PA, 19104, USA
SOURCE: Journal of General Virology (1991), 72(3), 641-9
CODEN: JGVIAY; ISSN: 0022-1317
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In previous studies, the herpes simplex virus type 1 (HSV-1) mutant, **in1814**, which lacks the transinducing function of Vmw65, did not replicate in the trigeminal ganglia of mice following corneal inoculation but did establish a reactivatable latent infection in the ganglia 12 to 24 h after ocular infection. Since **in1814** did not replicate in vivo, the mol. events during the establishment phase of latent HSV-1 infection could be characterized without the complications of concurrent productive viral infection. In comparison to parental HSV-1 strain 17+, the expression of viral immediate early (IE), early and late genes and the levels of viral DNA in the trigeminal ganglia of mice following **in1814** infection were greatly reduced. However, accumulation of latency-assocd. transcripts, a prominent feature of latent HSV-1 infection, occurred in a wild-type fashion. Furthermore, low levels of viral gene expression and an increase in the level of viral DNA in the

in1814-infected ganglia were not detected until 1 to 2 days after the establishment of HSV-1 latency. Thus, IE gene expression and replication of viral DNA in the trigeminal ganglia are not prerequisites for the establishment of HSV-1 latency. These results suggest that the pathways leading to productive and latent infections in neurons may diverge at an early stage of the host-HSV-1 interaction and that the level of viral IE gene expression has a key role in detg. the outcome of infection.

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          7671 "EQUINE"
           103 "EQUINES"
          7731 "EQUINE"
                 ("EQUINE" OR "EQUINES")
         20681 "HERPES"
        273942 "VIRUS"
         52435 "VIRUSES"
        283247 "VIRUS"
                 ("VIRUS" OR "VIRUSES")
        729057 "GENE"
        275035 "GENES"
        771619 "GENE"
                 ("GENE" OR "GENES")
       1167881 "12"
L8           0 "EQUINE HERPES VIRUS GENE 12"
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=> "EHV gene 12"
           474 "EHV"
             4 "EHVS"
           474 "EHV"
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        275035 "GENES"
        771618 "GENE"
                 ("GENE" OR "GENES")
       1167881 "12"
L9           0 "EHV GENE 12"
                 ("EHV"(W)"GENE"(W)"12")

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LOGOFF? (Y)/N/HOLD:n

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LOGOFF? (Y)/N/HOLD:y
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Roddie C.
CORPORATE SOURCE: Department of Dermatology, Medical University of Lodz,
Lodz, Pol.
SOURCE: Immunology (2001), 104(4), 468-475
CODEN: IMMUAM; ISSN: 0019-2805
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Herpes simplex virus (HSV) is known to possess several mechanisms whereby it can evade the normal host immune defenses. Here, the expression of the immunosuppressive cytokine, interleukin (IL)-10, was monitored following infection of a murine keratinocyte cell line (PAM-212) and compared with the expression of 2 proinflammatory cytokines: IL-1.alpha. and tumor necrosis factor (TNF)-.alpha.. The PAM-212 cells were infected at a multiplicity of 0.5 with a clin. isolate of HSV type 1, and the mRNA of the 3 cytokines was assessed by semiquant. reverse transcription-polymerase chain reaction (RT-PCR) over the following 24 h. By 12 h postinfection the amt. of IL-10 mRNA had increased to 5-fold greater than that found in uninfected cells, and this elevated level was maintained until at least 24 h postinfection. In contrast, IL-1.alpha. and TNF-.alpha. mRNAs were not up-regulated by the HSV infection. Immunostaining with an IL-10 monoclonal antibody (mAb) revealed that cytoplasmic IL-10 protein had increased by 6-12 h postinfection. This quantity was further increased at 24 h postinfection, when the viral cytopathic effect was apparent. Viral replication was necessary, but not sufficient on its own, for IL-10 induction. Expts. with **HSV mutants** lacking functional transactivating factors suggested that the viral transactivating proteins ICP-0 and VP-16 may be necessary for HSV-induced IL-10 expression. Thus, the up-regulation in the expression of IL-10 mRNA and protein induced by HSV early in the infection of keratinocytes represents a specific response and may be part of the viral strategy to avoid local immune defense mechanisms in the skin.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:239298 CAPLUS
DOCUMENT NUMBER: 128:279564
TITLE: Herpes simplex virus attenuated strains with modified immediate early genes
INVENTOR(S): DeLuca, Neal A.
PATENT ASSIGNEE(S): University of Pittsburgh of the Commonwealth System of Higher Education, USA; DeLuca, Neal A.
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9815637	A1	19980416	WO 1997-US8681	19970522

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC,

the subsequent phenotypic anal. of the resulting mutants, should provide insights into how these proteins function in the HSV life cycle and also into the specific macromol. events that are altered or perturbed in cells infected with virus strains blocked very early in infection. This approach may also provide a rational basis to assess the efficacy and safety of **HSV mutants** for use in gene transfer expts.
In this study, the authors generated and examd. the phenotype of an **HSV mutant** simultaneously mutated in the **ICP4**, ICP27, and ICP22 genes of HSV. Unlike mutants deficient in **ICP4** (d120), **ICP4** and ICP27 (d92), and **ICP4** and ICP22 (d96), mutants defective in **ICP4**, ICP27, and ICP22 (d95) were visually much less toxic to Vero and human embryonic lung cells. Cells infected with d95 at a multiplicity of infection of 10 PFU per cell retained a relatively normal morphol. and expressed genes from the viral and cellular genomes for at least 3 days postinfection. The other mutant backgrounds were too toxic to allow examn. of gene expression past 1 day postinfection. However, when cell survival was measured by the capacity of the infected cells to form colonies, d95 inhibited colony formation similarly to d92. This apparent paradox was reconciled by the observation that host cell DNA synthesis was inhibited in cells infected with d120, d92, d96, and d95. In addn., all of the mutants exhibited pronounced and distinctive alterations in nuclear morphol., as detd. by electron microscopy. The appearance of d95-infected cells deviated from that of uninfected cells in that large circular structures formed in the nucleus. D95-infected cells abundantly expressed ICP0, which accumulated in fine punctate structures in the nucleus at early times postinfection and coalesced or grew to the large circular objects that were revealed by electron microscopy. Therefore, while the abundant accumulation of ICP0 in the absence of **ICP4**, ICP22, and ICP27 may allow for prolonged gene expression, cell survival is impaired, in part, as a result of the inhibition of cellular DNA synthesis.

L4 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:645381 CAPLUS
DOCUMENT NUMBER: 121:245381
TITLE: Antitumor activity and reporter gene transfer into rat brain neoplasms inoculated with herpes simplex virus vectors defective in thymidine kinase or ribonucleotide reductase
AUTHOR(S): Boviatsis, Efstathios J.; Scharf, Jeremiah M.; Chase, Maureen; Harrington, Karen; Kowall, Neal W.; Breakefield, Xandra O.; Chiocca, E. Antonio
CORPORATE SOURCE: Department of Surgery, Harvard Medical School, Charlestown, MA, 02129, USA
SOURCE: Gene Therapy (1994), 5(1), 323-31
CODEN: GETHEC; ISSN: 0969-7128
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Herpes simplex virus (**HSV**) **mutants** or recombinant vectors might be useful oncolytic agents. Three general types of HSV vectors can be potentially used for this purpose: (1) mutants in viral transcription factors, such as ICP0 and **ICP4**; (2) mutants in enzymes involved in nucleic acid metab., such as thymidine kinase (TK) and ribonucleotide reductase (RR); and (3) mutants in neurovirulence factors, such as .gamma.34.5. We tested the destructive ability of each type against rat 9L gliosarcoma cells in culture. We found that the HSV vectors defective in TK or RR were more efficient at tumor cell lysis in

culture than the other types of HSV vectors. This increased efficiency provided the rationale for evaluating the TK and RR mutants in vivo following their stereotactic inoculation into 9L gliosarcomas implanted in rat brains. We employed the X-gal enzymic histochem. assay to show that HSV-mediated lacZ gene expression was present in cells within the tumor mass in a relatively selective fashion. Immunoreactive HSV capsid and core antigens were present both in cells within the tumor, as well as in cells such as neurons and astrocytes, directly adjacent to the tumor mass. Long-term survival studies revealed that rats treated with either the TK or RR mutant lived significantly longer than control rats ($p = 0.014$, Kruskal-Wallis one-way anal. of variance). These results indicate that HSV vectors, defective in enzymes needed in nucleic acid metab., can preferentially mediate lacZ gene expression in cells within the tumor. Furthermore, these vectors can enter into endogenous neural cells (accounting for the detection of viral capsid and core antigens), but probably mediate very low levels of lacZ gene expression, presumably due to shut-off of the lacZ gene promoter. The tumoricidal activity of these vectors results in significant prolongation in the survival of rats injected with each mutant. A model of HSV vector infection and propagation within the tumor and adjacent brain is discussed.

L4 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:649618 CAPLUS
DOCUMENT NUMBER: 115:249618
TITLE: Expression of genes in central nervous system cells using herpes simplex virus mutants with deletions in genes for viral replication
INVENTOR(S): Breakfield, Xandra O.; Martuza, Robert L.
PATENT ASSIGNEE(S): General Hospital Corp., USA
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 453242	A1	19911023	EP 1991-303387	19910416
EP 453242	B1	19960821		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2039921	AA	19911017	CA 1991-2039921	19910405
JP 07095885	A2	19950411	JP 1991-110907	19910416
AT 141517	E	19960915	AT 1991-303387	19910416
ES 2090243	T3	19961016	ES 1991-303387	19910416

PRIORITY APPLN. INFO.: US 1990-508731 19900416
AB An in vivo gene transfer technique for introducing and expressing a gene into a central nervous system (CNS) cell using a herpes simplex virus-1 (HSV-1) vector is described. The vector is derived from an HSV-1 having a mutation in the genes involved in viral replication, e.g., the immediate early genes that encode the infected cell proteins (ICPs) 0, 4, 22, 27, and/or 47, or the early genes that encode thymidine kinase or DNA polymerase. The method and the vectors can be used for treating a neurol. deficiency of the CNS. Three HSV-1 mutant vectors, 7134, GAL4, and RH105, that carried the lacZ gene were intracerebrally inoculated into rats and

the brain sections of the rats were processed histochem. and assessed for the presence of the .beta.-galactosidase activity. The mutant vectors were relatively nonpathogenic and the animals showed less behavior abnormalities, as compared to a wild-type vector HSV-1 KOS.

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:527672 CAPLUS
DOCUMENT NUMBER: 113:127672
TITLE: Quantitative polymerase chain reaction analysis of herpes simplex virus DNA in ganglia of mice infected with replication-incompetent mutants
AUTHOR(S): Katz, Jonathan P.; Bodin, Ethan T.; Coen, Donald M.
CORPORATE SOURCE: Dep. Biol. Chem. Mol. Pharmacol., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Journal of Virology (1990), 64(9), 4288-95
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To study the roles of viral genes in the establishment and maintenance of herpes simplex virus (HSV) latency, the authors have developed a polymerase chain reaction assay that is both quant. and sensitive. Using this assay, the authors analyzed the levels of viral DNA in trigeminal ganglia of mice inoculated corneally with **HSV mutants** that are defective for virus replication at one or more sites in mice and for reactivation upon ganglionic explant. Ganglia from mice infected with thymidine kinase-neg. mutants, which replicate at the site of inoculation and establish latency but do not replicate acutely in ganglia or reactivate upon explant, contained a range of levels of HSV DNA that overlapped with the range found in ganglia latently infected with wild-type virus. On av., these mutant-infected ganglia contained one copy of HSV DNA per 100 cell equiv. (.apprx.104 mols.), which was 50-fold less than the av. for wild-type virus. Ganglia from mice infected with a ribonucleotide reductase deletion mutant, which is defective for acute replication and reactivation upon ganglionic explant, also contained on av. one copy of HSV DNA per 100 cell equiv. The authors also detected substantial nos. of HSV DNA mols. (up to .apprx.103) in ganglia of mice infected with an **ICP4** deletion mutant and other replication-neg. mutants that are severely impaired for viral DNA replication and gene expression. These results raise the possibility that such mutants can establish latency, which could have important implications for mechanisms of latency and for vaccine and antiviral drug development.

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:173198 CAPLUS
DOCUMENT NUMBER: 112:173198
TITLE: Variable requirements for herpes simplex virus immediate-early proteins in the expression of the adenovirus E2 gene
AUTHOR(S): Bachenheimer, Steven L.; Elshiekh, Nina
CORPORATE SOURCE: Sch. Med., Univ. North Carolina, Chapel Hill, NC, 27599, USA
SOURCE: Virology (1990), 175(1), 338-42
CODEN: VIRLAX; ISSN: 0042-6822
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Regulation of the adenovirus E2 gene by trans-activating proteins encoded by herpes simplex virus was investigated. Coinfection of Vero cells was performed with Ad5 dL312 (an E1 deletion mutant) and either wildtype

HSV, mutant virus encoding a temp.-sensitive **ICP4** protein (tsK), or mutants carrying deletions in the **ICP4** (d120) or ICP0 (dL .times. 3.1) gene. As detected by the presence of E2 mRNA, or the product of the E2 gene, 72-kDa DNA binding protein (DBP), functional **ICP4** was sufficient for expression of the E2 gene. Regulation of E2 gene expression was at the level of transcription activation as judged by nuclear run-on assay. In contrast to results when Vero cells were coinfected, expression of 72-kDa DBP in CN3 cells, carrying an integrated copy of the E2 gene, required expression of both HSV immediate early proteins. These results suggest that the DNA-protein organization of the target gene sequence may play a significant role in the ability of viral regulatory proteins to activate expression of heterologous as well as homologous genes.

L4 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:191067 CAPLUS
DOCUMENT NUMBER: 110:191067
TITLE: The herpes simplex virus immediate-early protein, **ICP4**, is required to potentiate replication of human immunodeficiency virus in CD4+ lymphocytes
AUTHOR(S): Albrecht, Mary A.; DeLuca, Neal A.; Byrn, Randal A.; Schaffer, Priscilla A.; Hammer, Scott M.
CORPORATE SOURCE: New England Deaconess Hosp., Harvard Med. Sch., Boston, MA, 02215, USA
SOURCE: J. Virol. (1989), 63(5), 1861-8
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The interaction of human immunodeficiency virus (HIV) and herpes simplex virus (HSV) was investigated in an acute whole-virus coinfection system. CD4+ lymphoid CEM cells were infected with HIV-1 and, 24 h later, superinfected with HSV-1 (strain KOS) or **HSV mutants** possessing defined deletions in genes specifying the immediate-early transcriptional regulatory proteins ICP0, **ICP4**, or ICP27. Marked potentiation of HIV replication was demonstrated with the KOS strain, the ICP0 mutant, and the ICP27 mutant, but not with the **ICP4** mutant, indicating that **ICP4** is essential and ICP0 and ICP27 are nonessential for this effect. Thus, HSV can be a potent stimulator of HIV replication and gene expression in coinfected CD4+ cells through the activity of the HSV regulatory protein **ICP4**.

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L3 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:920110 CAPLUS
DOCUMENT NUMBER: 136:165922
TITLE: Infection of murine keratinocytes with herpes simplex virus type 1 induces the expression of interleukin-10, but not interleukin-1.alpha. or tumor necrosis factor-.alpha.
AUTHOR(S): Zak-Prelich, Malgorzata; Halliday, Katrina E.; Walker, Craig; Yates, Catherine M.; Norval, Mary; Mckenzie,

L4 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:121544 CAPLUS
DOCUMENT NUMBER: 126:223708
TITLE: Herpes simplex virus immediate-early proteins ICP0 and
ICP4 activate the endogenous human .alpha.-globin gene in nonerythroid cells
AUTHOR(S): Cheung, Peter; Panning, Barbara; Smiley, James R.
CORPORATE SOURCE: Institute for Molecular Biology and Biotechnology, McMaster University, Hamilton, ON, L8N 325, Can.
SOURCE: Journal of Virology (1997), 71(3), 1784-1793
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Globin genes are normally expressed only in erythroid cell lineages. However, the authors found that the endogenous .alpha.-globin gene is activated following infection of human fibroblasts and HeLa cells with herpes simplex virus (HSV), leading to accumulation of correctly initiated transcripts driven by the .alpha.-globin promoter. The .alpha.1- and .alpha.2-globin genes were both induced, but expressed of .beta.- or .zeta.-globin genes could not be detected. Expts. using **HSV mutants** showed that null mutations in the genes encoding the viral immediate-early proteins **ICP4** and ICP22 reduced induction approx. 10-fold, while loss of ICP0 function had a smaller inhibitory effect. Transient transfection expts. showed that ICP0 and **ICP4** are each sufficient to trigger detectable expression of the endogenous gene, while ICP22 had no detectable effect in this assay. **ICP4** also strongly enhanced expression of transfected copies of the .alpha.2-globin gene. In contrast, the adenovirus E1a protein did not activate the endogenous gene and inhibited expression of the plasmid-borne .alpha.2-globin gene. Previous studies have led to the hypothesis that chromosomal .alpha.-globin genes are subject to chromatin-dependent repression mechanism that prevents expression in nonerythroid cells. The data suggest that HSV ICP0 and **ICP4** either break or bypass this cellular gene silencing mechanism.

L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:495342 CAPLUS
DOCUMENT NUMBER: 125:190329
TITLE: Prolonged gene expression and cell survival after infection by a herpes simplex virus mutant defective in the immediate-early genes encoding **ICP4**, ICP27, and ICP22
AUTHOR(S): Wu, Naxin; Watkins, Simon C.; Schaffer, Priscilla A.; DeLuca, Neal A.
CORPORATE SOURCE: Department Molecular Genetics and Biochemistry, University Pittsburgh School Medicine, Pittsburgh, PA, 15261, USA
SOURCE: Journal of Virology (1996), 70(9), 6358-6369
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Very early in infection, herpes simplex virus (HSV) expresses four immediate-early (IE) regulatory proteins, **ICP4**, ICP0, ICP22, and ICP27. The systematic inactivation of sets of the IE proteins in cis, and